Predominance of herpes simplex virus type 1 from patients with genital herpes in Nova Scotia

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The epidemiology of genital herpes is changing with evidence to suggest an increasing incidence of herpes simplex virus type 1 (HSV-1) infections. The results of 6529 HSV genital cultures taken between April 1998 and December 2001 were reviewed. Overall, HSV-1 was recovered more often than HSV-2; 1213 versus 1045. This trend was particularly striking in young women 30 years of age or less, in whom 70.8% of isolates were HSV-1. In men of the same age range, 45% of isolates were HSV-1. The proportion of women with HSV-1 declined from 73.7% in those younger than 31 years of age to 4.5% in those older than 60 years of age.

These observations have important implications. The decline in the relative proportion of HSV-1 isolates from young adults may be the result of changing sexual practices, changing susceptibility or increased exposure to HSV-1 during vaginal intercourse. In this setting HSV-2 vaccines may be less likely to produce the desired reduction in the overall prevalence of genital herpes infections.

Key Words: *Genital herpes; Herpes simplex virus type-1*

Prédominance de l'herpès simplex virus type I chez des patients souffrant d'herpès génital en Nouvelle-Écosse

RÉSUMÉ : L'épidémiologie de l'herpès génital évolue et les observations indiquent une augmentation de l'incidence d'infections à herpès simplex virus type I (HSV 1). Les résultats de 6 529 cultures génitales de HSV prélevées entre les mois d'avril 1998 et décembre 2001 ont été passés en revue. Dans l'ensemble, le HSV 1 a été décelé plus souvent que le HSV 2; soit 1 213 cultures contre 1 045.

Cette tendance était particulièrement frappante chez les jeunes femmes de moins de 30 ans chez lesquelles 70,8 % des isolats étaient positifs pour le HSV 1 par rapport à 45 % pour les hommes du même groupe d'âge. La proportion de femmes positives pour le HSV 1 est passée de 73,7 % chez les femmes de moins de 31 ans à 4,5 % chez celles qui avaient plus de 60 ans.

Ces observations ont une incidence importante. En effet, la baisse de la proportion relative d'isolats de HSV 1 décelés chez de jeunes adultes peut résulter d'une modification des pratiques sexuelles, d'un changement de la susceptibilité ou d'une exposition accrue au HSV 1 durant les rapports sexuels vaginaux. Dans ces circonstances, les vaccins anti HSV 2 seraient moins susceptibles de produire la réduction souhaitée de la prévalence globale des infections herpétiques génitales.

Many factors have contributed to the changing epidemiology of sexually transmitted diseases (STDs) in the past decade. Changes in sexual practices, improved diagnosis and more effective treatments have dramatically reduced the incidence of chlamydia, gonorrhea and syphilis (1). On the other hand, in many countries the incidence of genital herpes (GH) infections has not declined. In the United States, the number of physician office visits for GH has increased markedly since 1966 (1). There are likely several reasons why significant declines have not been observed: the period of infectivity may extend over many years, GH may be less effectively prevented by condom use, diagnosis of subclinical infections is technically difficult, and no curative treatments are available. Many patients have numerous asymptomatic recurrences and are unable to identify periods of increased infectivity.

There is evidence that the relative prevalence of herpes simplex virus type 1 (HSV-1) and HSV-2 genital infections may be changing. Recent studies from Scandinavia and the United States suggest that HSV-1 infections are increasingly prevalent (2-5). We reviewed the results of genital cultures performed at our hospital over a 30-month period to determine whether this is also the case in Nova Scotia.

MATERIALS AND METHOD

The laboratory at the Queen Elizabeth II Health Sciences Centre provides the only virus culture testing in Nova Scotia. The number of cultures, the site, the patient's age and sex, and the culture results were abstracted from the authors' laboratory information system. Only those cultures performed on patients older than 16 years of age where the age and sex were stated on the requisition are included in the analysis. Testing was performed between April 1998 and December 2001. The patient population consisted primarily of patients seen in the offices of physicians practising in the community.

Tissue culture

A549 cells (ATCC CCL-185), a human lung carcinoma cell line, were grown at 37°C in RPMI 1640 medium (Gibco Laboratories, USA) supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL of penicillin and 50 U/mL of streptomycin. Cell monolayers were prepared in conventional culture tubes. When the monolayers were reaching 75% confluence, usually in 24 h, the growth medium in each culture was replaced with 1 mL of RPMI 1640 medium supplemented with 2% fetal bovine serum, 50 U/mL of ampicillin, 12.5 U/mL of netilmycin and 5 U/mL of amphotericin B (maintenance medium).

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Virus culture and idenfication

Genital swab specimens taken with the Micro Collection and Transport System (NCS Diagnostics, Etobicoke) were submitted for culture. An aliquot (0.25 mL) of the specimen in viral transport medium was used to inoculate two A549 monolayers. The cultures were kept at 37°C and examined daily for seven days or until 50% of the monolayer exhibited cytopathic effect. The cultures were then harvested for typing by immunofluorescence with the MicroTrak HSV-1/HSV-2 Culture Identification/Typing Test (Trinity Biotech plc, Ireland). Cultures without cytopathic effect were reported as negative after seven days.

RESULTS

Over the 30-month period between April 1998 and December 2001, 6529 genital swabs were submitted to the author's laboratory for HSV isolation (Table 1). The patient's sex was omitted on 36 requisitions and the age was not indicated on 112. In total, 2258 (34.6%) swabs were positive. Twelve hundred thirteen (53.7%) swabs were HSV-1 isolates. HSV-1 was recovered more often than HSV-2 in specimens from women (1041 of 1790 [58.2%]). In specimens from women younger than 31 years of age, 780 of 1103 (70.8%) isolates were HSV-1. Of positive cultures from men of the same age, 99 of 220 (45%) were HSV-1 isolates.

The percentage of positive genital cultures from which HSV-1 was isolated is shown in Table 1. The proportion of isolates from women that were HSV-1 declined from 73.7% in those between the ages of 16 and 20 years to 4.5% in those over the age of 60 years. There was a similar but less dramatic decline in specimens from men, where the relative proportion of HSV-1 isolates declined from 53.8% in those between the ages of 16 and 20 years to 20.0% in those older than 60 years of age.

DISCUSSION

We found that HSV-1 is the predominant isolate from genital specimens submitted in Nova Scotia. Others have also reported a relative increase in HSV-1 isolation rates. In a review of cultures submitted to a Kentucky virology laboratory, Ribes et al (4) noted a trend of increasing HSV-1 rates in both men and women. Between 1994 and 1999, the proportion of genital cultures positive for HSV-1 rose from approximately 27% to 45%. Lowhagen et al (6) isolated 97 strains of HSV from patients presenting to STD clinics in Sweden between 1995 and 1999. Forty-four per cent were due to HSV-1. When they examined the most recent seroconversions in patients with GH, 64% were due to HSV-1 infections.

Nilsen and Myrmel (2) studied women presenting to an STD clinic in Bergen, Norway. They found that up to 90% of younger women with primary or initial GH disease had HSV-1 infections. Vyse et al (7) showed that HSV-1 seroprevalence in 10- to 14-year-olds in the United Kingdom declined between 1987 and 1995. They found that HSV-1 seroprevalence increased in individuals between 15 and 24 years of age, suggesting HSV-1 transmission in adolescence and young adulthood may be due to sexual transmission (7). Fifty-four per cent of women between the ages of 25 and 30 years had HSV-1 antibodies. They concluded that a significant proportion of the HSV-1 seropositivity was due to genital infection and that HSV-1 was the predominant cause of GH in the United Kingdom.

GH simplex infections continue to cause considerable physical and psychological morbidity, even as other STDs such as chlamydia and gonorrheal infections decline. It is believed that the majority of infections are transmitted from asymptomatic people (8-11). The high prevalence of GH infections, the long period of infectivity, viral shedding without symptoms and incomplete protection with condom use contribute to its continued spread (12,13). In addition, transmission may occur by oral-genital spread as well as by the genital-genital route. HSV-1 is commonly present in the oral cavities of asymptomatic individuals (14-16). Earlier studies suggested that between 10% and 30% of GH infections were due to HSV-1 (17). In a study by Langenberg et al (18), the overall rate of HSV-2 infection was 5.1 cases per 100 person-years. The rate of new HSV-1 infections averaged 1.6 cases per 100 patient years. However, only one-third of these cases were proven to be genital infections. It is thought that the majority of these cases were acquired as a result of oral-genital spread; however,

TABLE 1
Summary of the results of genital source herpes simplex virus (HSV) cultures submitted to the Queen Elizabeth II Health Sciences Centre between April 1998 and December 2001

	Age ranges (years)										
	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	>60	Total
Women											
HSV-1	309	321	150	99	87	39	15	15	4	2	1088
HSV-2	110	165	48	125	88	71	43	34	23	42	766
Cultures negative	508	767	526	393	365	251	157	114	51	123	3433
Percentage of positive cultures yielding HSV-1	73.7%	66.0%	75.8%	44.2%	49.7%	35.5%	25.9%	30.6%	14.8%	4.5%	5287
Men											
HSV-1	21	50	28	20	26	10	4	6	1	6	17
HSV-2	18	48	55	42	37	29	15	21	7	24	305
Cultures negative	118	232	129	119	111	88	59	52	31	77	1083
Percent of positive cultures yielding HSV-1	53.8%	51.0%	33.7%	32.3%	41.3%	25.6%	21.1%	22.2%	12.5%	20.0%	1562
Total											
Positive cultures	459	585	281	286	238	149	77	76	35	74	2343
Negative cultures	626	1002	658	514	478	339	216	167	83	200	4542
Cultures submitted	1085	1587	939	800	716	488	293	243	118	274	6885

the exact proportion of spread by different forms of sexual contact had not been fully elucidated. Clearly, some HSV-1 infections may be acquired from vaginal intercourse.

Unfortunately, we do not have access to information on the relative frequency of isolation of HSV-1 and HSV-2 from genital specimens before April 1998, and we do not have data on whether the cultures were from primary or recurrent infections. As a result, it is not possible to say how closely our numbers reflect the relative proportion for incident infections, although we were unable to exclude duplicate results from our evaluation because HSV-2 infections recur more often and, if anything, this would bias observations toward null. Assuming that our numbers represent a fair surrogate marker of relative incidence, how are the differences explained? In some settings, the frequency of oral HSV-1 infections in childhood may be declining. As a result, many more individuals reach adulthood without specific immunity to HSV-1 and may be more susceptible to infection and more likely to present with a clinically apparent infection (19,20).

Changing sexual practices may be contributing to the shift toward more HSV-1 infections. We do not have information on the sexual practices of Nova Scotians with GH that may offer insight into our findings. The higher proportion of young women than men who were infected with HSV-1 versus HSV-2 may reflect a greater susceptibility of the female genital tract or a greater propensity to transmit herpes viruses by cunnilingus compared with fellatio. We are unaware of studies that have examined this question. Such studies would be useful to better understand oral-genital transmission between couples.

The predominance of HSV-1 in GH cultures has a number of important implications. The information we give to patients may need to change because the likely mode of acquisition may be different and HSV-1 infections are less likely to recur (21-27). These results also raise questions about the utility of type-specific antibodies to diagnose someone as 'genitally infected'. These findings also make the use of HSV-2 serological population-based studies much less useful for determining the prevalence of GH. Additionally, vaccine development has largely centred around HSV-2 (18,28-31). Our findings suggest that such vaccines may be less valuable unless they also provide excellent protection from HSV-1.

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